1. NAME OF THE MEDICINAL PRODUCT

ZIPRONAT PLUS (CIPROFLOXACIN AND DEXAMETHASONE EYE DROPS)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition:

Each ml contains
Ciprofloxacin Hydrochloride USP
Eq to Ciprofloxacin - --- - 0.3% W/V
Dexamethasone - USP - 0.1% W/V
Benzolkonium Chloride NF (As Preservative) - --- - 0.01%

Excipients with known effect:
Each ml contains 0.1 mg of Benzalkonium Chloride and 20 mg Hydroxy Propyl Beta Cyclodextrin (HPBCD)

3. PHARMACEUTICAL FORM

Ophthalmic solution
A clear colorless solution.
pH ranging from 4.0 to 5.0.

4. Clinical particulars

4.1 Therapeutic indications

Indicated in adults and children above 2 years for post-operative steroid responsive inflammatory ocular conditions when bacterial ocular infections or a risk of bacterial ocular infections exists. It is indicated for bacterial corneal ulcers and conjunctivitis.

4.2 Posology and method of administration

For topical ocular instillation.

Adults and children above 2 year of age:

Severe inflammations require 1 to 2 drops instilled into the eye every thirty to sixty minutes until a satisfactory response occurs. When a favourable response observe, reduce the dosage towards 1 drop every four hours.
The frequency of instillation of drops and the duration of treatment will vary depending upon the severity of the underlying condition and the response to treatment.
Therapy should not be used for longer than one week (as it contains dexamethasone, a topical corticosteroid) except under medical/ophthalmic supervision, with regular checks of intraocular pressure (IOP).
Or, as directed by Physician/Ophthalmologist.

Paediatric Population

The safety and efficacy of this product has not been established in children below 2 years of age.

Method of Administration

- For ocular use only.
- Not for injection.
- Do not touch tip of the vial to finger or to eye(s)/eyelids or to any other surface since this may contaminate the solution.
- If eye irritation occurs after using this product, discontinue the use and consult the Physician.
- Contact lenses should be removed before instillation of the eye drops and may be reinserted after 15 minutes.
- If more than one topical ophthalmic medicinal product is being used, the medicinal products should be instilled 5 to 15 minutes apart. Eye ointments should be administered last.
- Nasolacrimal occlusion or gently closing the eyelid after administration is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse effects.
- Discard unused portion of eye drop, if any, after one month of first opening the vial (even though expiry date is longer).
- Follow the directions mentioned on the container label.

4.3 Contraindications

Ciprofloxacin and Dexamethasone Eye Drops are contraindicated in:

- Patient with known hypersensitivity to the ciprofloxacin or to dexamethasone or to any other quinolone or to any of the excipients listed in section 6.1.
- Vaccinia, varicella, or other viral diseases of cornea and conjunctiva (except herpes zoster keratitis).
- Herpes simplex keratitis.
- Fungal diseases of ocular structures or untreated parasitic eye infections.
- Mycobacterial ocular infections.

4.4 Special warnings and precautions for use

Ciprofloxacin

Hypersensitivity: Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, were observed in patients receiving treatment based on systematically administered quinolones. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnoea, urticaria and itching. Only a few patients had a history of hypersensitivity reactions.

Serious acute hypersensitivity reactions to ciprofloxacin may require immediate emergency treatment. Oxygen and airway management should be administered where clinically indicated. This product should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

Bacterial Resistance: When using ciprofloxacin eye drops one should take into account the risk of rhinopharyngeal passage which can contribute to the occurrence and the diffusion of bacterial resistance.

Superinfection: As with all antibacterial preparations prolonged use may lead to overgrowth of nonsusceptible bacterial strains or fungi. If superinfection occurs, appropriate

therapy should be initiated.

Tendinopathy: Tendon inflammation and rupture may occur with systemic fluoroquinolone therapy including ciprofloxacin, particularly in elderly patients and those treated concurrently with corticosteroids. Therefore, treatment with Eye Drops should be discontinued at the first sign of tendon inflammation.

Dexamethasone

Prolonged use of topical ophthalmic corticosteroids may result in ocular hypertension and/or glaucoma, with damage to the optic nerve, reduced visual acuity, visual field defects and posterior subcapsular cataract formation. In patients receiving prolonged ophthalmic corticosteroid therapy,IOP and the lens should be checked routinely and frequently, particularly in patients with a history or presence of glaucoma. This is especially important in paediatric patients as the risk of corticosteroidinduced ocular hypertension may be greater in children and may occur earlier than in adults. The risk of corticosteroid-induced raised IOP and/or cataract formation is increased in predisposed patients (e.g., diabetes).

In patients receiving systemic corticosteroids, new-onset or exacerbation of pre-existing diabetes mellitus may occur. Because of the possibility of reduced glucose tolerance/diabetes mellitus with topical ophthalmic corticosteroids, caution is recommended when administering this medicinal product to patients with a personal or family history of diabetes. Cushing's syndrome and/or adrenal suppression associated with systemic absorption of ocular dexamethasone may occur after intensive or long-term continuous therapy in predisposed patients, including children and patients treated with CYP3A4 inhibitors (including ritonavir and cobicistat). In these cases, treatment should be progressively discontinued. Corticosteroids may reduce resistance to and aid in the establishment of bacterial, viral, fungal or parasitic infections and mask the clinical signs of infections. In such cases antibiotic therapy is mandatory. Fungal infection should be suspected in patients with persistent corneal ulceration and corticosteroids therapy should be discontinued if fungal infection occurs.

Topical ophthalmic corticosteroids may slow corneal wound healing. Topical NSAIDs are also known to slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.

In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical corticosteroids.Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may be cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Benzalkonium Chloride (BKC) as Preservative: Benzalkonium chloride is used as preservative in this medicinal product which has been reported to cause eye irritation, symptoms of dry eyes and may affect the tear film and corneal surface. This medicinal product should be used with caution in dry eye patients and in patients where the cornea may be compromised. From the limited data available, there is no difference in the adverse event profile in children compared to adults. However, eyes in children generally show a stronger reaction for a given stimulus than the adult eye. Irritation may have an effect on treatment adherence in children.

Contact Lenses: The wearing of contact lenses is discouraged during treatment of an ocular inflammation. Contact lenses may absorb benzalkonium chloride and these should be removed before instilling this eye drops but may be reinserted after 15 minutes.

In patients with corneal ulcer and frequent administration of ciprofloxacin eye drops, white topical ocular precipitates (medication residue) have been observed which resolved after continued application of product. The precipitate does not preclude the continued application of the eye drops nor does it adversely affect the clinical course of the recovery process. The onset of the precipitate was within 24 hours to 7 days after starting therapy. Resolution of the precipitate varied from
immediately to 13 days after therapy commencing.

Paediatric Population

Ciprofloxacin

The clinical experience in children less than one year old, particularly in neonates is very limited. The use of ciprofloxacin eye drops in neonates with ophthalmia neonatorum of gonococcal or chalamydial origin is not recommended as it has not been evaluated in such patients. Neonates with ophthalmia neonatorum should receive appropriate treatment for their condition.

Dexamethasone

There is no evidence of safety in use in children under two years of age. In paediatric patients, the risk of corticosteroid-induced ocular hypertension may be greater and may occur earlier than in adults.

4.5 Interaction with other medicinal products and other forms of interaction

If more than one topical ophthalmic medicinal product is being used, the medicines must be administered at least 5 minutes apart. Eye ointments should be administered last.

Ciprofloxacin

Specific drug interaction studies have not been conducted with ophthalmic ciprofloxacin. Given the low systemic concentration of ciprofloxacin following topical ocular administration of the product, drug interactions are unlikely to occur.

Dexamethasone

No interaction studies have been performed.

NSAIDs: Concomitant use of topical steroids and topical NSAIDs may increase the potential for corneal healing problems.

CYP3A4 Inhibitors (including ritonavir and cobicistat): Concomitant use may decrease dexamethasone clearance resulting in increased effects and adrenal suppression/Cushing's syndrome. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid effects.

Antidiabetic Drugs: The possibility of a higher need for hypoglycaemic medicinal products must be taken into consideration when administering dexamethasone eye drops to diabetic patients because the hypoglycaemic effect of these medicinal products may be reduced.

4.6 Pregnancy and Lactation

Pregnancy

There are no adequate or well-controlled studies evaluating the use of this medicinal product in pregnant women. Prolonged or repeated corticoid use during pregnancy has been associated with an increased risk of intra-uterine growth retardation. Infants born of

mothers who have received substantial doses of corticosteroids during pregnancy should be observed carefully for signs of hypoadrenalism. Studies in animals have shown reproductive toxicity with corticosteroids.
Ciprofloxacin and Dexamethasone Eye Drops is not recommended during pregnancy unless the clinical condition of the woman requires treatment and the therapeutic benefit is expected to outweigh the potential risk to the fetus.

Lactation
Orally administered ciprofloxacin is excreted in the human milk. It is unknown whether ciprofloxacin is excreted in human breast milk following topical ocular administration. It is unknown whether dexamethasone is excreted in human milk.
It is not likely that the amount of ciprofloxacin or dexamethasone in human milk would be capable of producing any clinical effects in the infant following maternal use of the product. However, a risk to the breastfeeding child cannot be excluded. Therefore, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
Studies have not been performed in humans to evaluate the effect of topical administration of ciprofloxacin or dexamethasone on fertility. Oral administration of ciprofloxacin in animals does not indicate direct harmful effects with respect to fertility. Dexamethasone had no adverse effects on female fertility in rat model.
There is limited clinical data to evaluate the effect of ciprofloxacin and dexamethasone on male or female fertility.

4.7 Effects on ability to drive and use machines

This product has no or negligible influence on the ability to drive and use machines. As with any topical ophthalmic medicinal product, temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs upon instillation, the patient must wait until the vision clears before driving or using machinery.

4.8 Undesirable effects

Ciprofloxacin
In clinical trials, the most frequently reported adverse drug reactions were ocular discomfort, dysgeusia and corneal deposits occurring approximately in 6%, 3% and 3% of patients respectively.

Tabulated summary of adverse reactions
The adverse reactions listed below are classified according to the following convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000),very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each frequency-grouping, adverse reactions are presented in order of decreasing seriousness. These adverse
reactions have been observed during clinical trials and post-marketing experience with the ophthalmic use of ciprofloxacin eye drops.

System Organ Class	Adverse Reactions
Immune system disorders	Rare: hypersensitivity
Nervous system disorders	Uncommon: headache

	Rare: dizziness
Eye disorders	Common: corneal deposits, ocular discomfort, ocular hyperaemia Uncommon: keratopathy, punctate keratitis, corneal infiltrates, photophobia, visual acuity reduced, eyelid oedema, blurred vision, eye pain, dry eye, eye swelling, eye pruritus, lacrimation increased, eye discharge, eyelid margin crusting, eyelid exfoliation, conjunctival oedema, erythema of eyelid Rare: ocular toxicity, keratitis, conjunctivitis, corneal epithelium defect, diplopia, hypoaesthesia eye, asthenopia, eye irritation, eye inflammation, hordeolum

Ear and labyrinth disorders	Rare: ear pain
Respiratory, thoracic and mediastinal disorders	Rare: paranasal sinus hypersecretion, rhinitis
Gastrointestinal disorders	Common: dysgeusia Uncommon: nausea Rare: diarrhoea, abdominal pain
Skin and subcutaneous tissue disorders	Rare: dermatitis
Musculoskeletal and connective tissue disorders	Not known: tendon disorder

With locally applied fluoroquinolones (generalized) rash, toxic epidermolysis, dermatitis exfoliative, Stevens-Johnson syndrome and urticaria occur very rarely. Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial oedema, dyspnoea, urticaria, and itching.

Ruptures of the shoulder, hand, achilles, or other tendons that required surgical repair or resulted in prolonged disability have been reported in patients receiving systemic fluoroquinolones. Studies and post marketing experience with systemic fluoroquinolones indicate that the risk of these ruptures may be increased in patients receiving corticosteroids, especially geriatric patients and in tendons under high stress, including the achilles tendon. Clinical and post marketing data have not demonstrated a clear association between ciprofloxacin eye drops and musculoskeletal and connective tissue adverse reactions.

In isolated cases blurred vision, decreased visual acuity and medication residue have been observed with ophthalmic ciprofloxacin.

Moderate to severe phototoxicity has been observed in patients treated with systemic quinolones. Nevertheless, phototoxic reactions to ciprofloxacin are uncommon.

Dexamethasone

In clinical trials, the most common adverse reaction was ocular discomfort.

Tabulated list of adverse reactions The following adverse reactions are classified according to the

following convention: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), or not known (cannot be estimated from the available data). Within each
frequency-grouping, adverse reactions are presented in order of decreasing seriousness. The adverse reactions have been observed during clinical trials and post-marketing experience with topical dexamethasone.

System Organ Classification	Adverse Reactions
Immune system disorders	Not known: hypersensitivity
Endocrine disorders	Not known: Cushing's syndrome, adrenal suppression
Nervous system disorders	Uncommon: dysgeusia Not known: dizziness, headache
Eye disorders	Common: ocular discomfort Uncommon: keratitis, conjunctivitis, dry eye, vital dye staining cornea present, photophobia, vision, blurred, eye pruritus, foreign body sensation in eyes, lacrimation increased, abnormal sensation in eyes, eyelid margin crusting, eye irritation, ocular hyperaemia Not known: glaucoma, ulcerative keratitis, intraocular pressure increased, visual acuity reduced, corneal erosion, eyelid ptosis, eye pain, mydriasis

Prolonged topical ophthalmic corticosteroids may result in increased IOP with damage to the optic nerve, reduced visual acuity and visual field defects, and to posterior subcapsular cataract formation.
Due to the corticosteroid component, in diseases causing thinning of the cornea or sclera there is a higher risk for perforation especially after long treatments.
Corticosteroids may reduce resistance to and aid in the establishment of infections.
Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.
Corticosteroids may impair glucose tolerance, which can lead to new-onset or exacerbation of diabetes mellitus.

Reporting of Suspected Adverse Reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system

Reporting suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

4.9 **Overdose**

Long-term intensive topical use of corticosteroid may lead to systemic effects. No toxic effects are to be expected with an ocular overdose of this product or in the event of accidental oral ingestion of contents of the 1 bottle. A topical overdose of Eye Drops can be flushed/rinsed out from the eye (s) with lukewarm water

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Ciprofloxacin
Pharmacotherapeutic Group: Ophthalmologicals, antiinfectives, fluoroquinolones.
ATC Code: S01CA01

Mechanism of Action
This medicinal product contains ciprofloxacin, a broad-spectrum anti-infective agent that belongs to the fluoroquinolones group. The cidal and inhibitory activity of ciprofloxacin against bacteria results from an interference with the DNA gyrase, an enzyme needed by the bacterium for the synthesis of DNA. Thus the vital information from the bacterial chromosomes cannot be transcribed which causes a breakdown of the bacterial metabolism and thereby death of bacterial cell.

Bacterial Resistance: Fluoroquinolone resistance, particularly ciprofloxacin, requires significant genetic changes in one or more of five major bacterial mechanisms: a) enzymes for DNA synthesis, b) protecting proteins, c) cell permeability, d) drug efflux, or e) plasmid-mediated aminoglycoside 6'-Nacetyltransferase, AAC (6')-Ib. Fluoroquinolones, including ciprofloxacin, differ in chemical structure and mode of action from aminoglycosides, β-lactam antibiotics, macrolides, tetracyclines, sulfonamides, trimethoprim, and chloramphenicol. Therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin. The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary,expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Pharmacodynamic Effects
Ciprofloxacin has in vitro activity against a wide range of Gram-positive and Gram-negative bacteria.
Commonly susceptible species
Aerobic Gram-positive microorganisms
- Corynebacterium accolens
- Corynebacterium auris

- Corynebacterium propinquum
- Corynebacterium psudodiphtheriticum
- Corynebacterium striatum
- Staphylococcus aureus (methicillin susceptible - MSSA)
- Staphylococcus capitis
- Staphylococcus epidermidis (methicillin susceptible - MSSE)
- Staphylococcus hominis
- Staphylococcus saprophyticus
- Staphylococcus warneri
- Streptococcus pneumoniae
- Streptococcus viridans Group

Aerobic Gram-negative microorganisms
- Acinetobacter species
- Haemophilus influenzae
- Moraxella catarrhalis
- Pseudomonas aeruginosa
- Serratia marcescens

Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms:
- Staphylococcus aureus (methicillin resistant - MRSA)
- Staphylococcus epidermidis (methicillin resistant - MRSE)
- Staphylococcus lugdunensis

Inherently resistant organisms
Aerobic Gram-positive micro-organisms:
- Corynebacterium jeikium

Dexamethasone
Pharmacotherapeutic Group: Ophthalmologicals, anti-inflammatory agents. **ATC Code:** S01BA01.
Mechanism of Action
Dexamethasone has been shown to suppress inflammation by inhibiting multiple inflammatory
cytokines resulting in decreased edema, fibrin deposition, capillary leakage and migration of inflammatory cells.
Pharmacodynamic Effects
Dexamethasone is a synthetic corticosteroid with an anti-inflammatory and anti- allergic action.Dexamethasone helps in the resolution of the inflammatory response accompanying bacterial infection. Dexamethasone has more potent anti-inflammatory action compared to hydrocortisone(approximately 25:1) and prednisolone (approximately 5:1).

5.2 Pharmakokinetic properties

Ciprofloxacin
Ciprofloxacin ophthalmic solution is rapidly absorbed into the eye following topical ocular administration. Systemic levels are low following topical administration. Plasma levels of ciprofloxacin in human subjects following 2 drops of 0.3% ciprofloxacin solution every 2

hours for two days and then every four hours for 5 days ranged from non-quantifiable (<1.0 ng/ml) to 4.7 ng/ml. The mean peak ciprofloxacin plasma level obtained in this study is approximately 450-fold less than that seen following a single oral dose of 250 mg ciprofloxacin.
Dexamethasone
Dexamethasone
is absorbed rapidly after oral administration with a half-life of about 190 minutes.
Sufficient absorption may occur after topical application to the skin and eye to produce systemic
effects. In plasma dexamethasone protein binding is less than for most other corticosteroids.
Corticosteroids diffuse into tissue fluids and cerebrospinal fluid but transplacental diffusion in
significant amounts has not been demonstrated. Corticosteroids are metabilised in the liver the kidney and excrete in the urine. Intraocular penetration occurs in significant amounts and contributes to the effectiveness of dexamethasone in anterior segment inflammatory disease.

5.3 Preclinical Safety Data

Ciprofloxacin
Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential. Non-clinical developmental toxicity was observed only at exposures considered sufficiently in excess of the maximum human exposure, indicating little relevance to clinical use.
Dexamethasone
Repeat dose topical ocular safety studies with dexamethasone in rabbits have shown systemic corticosteroid effects. Such effects are considered to be unlikely when topical dexamethasone eye drops are used as recommended.
Dexamethasone was clastogenic in the **in vitro** human lymphocyte assay and **in vivo** in the mouse micronucleus assay at doses in excess of those obtained following topical application. Conventional carcinogenicity studies with dexamethasone eye drops have not been performed. Dexamethasone has been found to be teratogenic in animal models. Dexamethasone induced abnormalities of fetal development including cleft palate, intra-uterine growth retardation and effects on brain growth and development. The ocular administration of 0.1% dexamethasone also resulted in fetal anomalies in rabbits. Dexamethasone had no adverse effects on female fertility in a chorionic gonadotropin primed rat model.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzalkonium chloride, Disodium EDTA, Sodium chloride, Hydroxyl Propyl Beta Cyclodextrin (HPBCD), Sodium dihydrogen Ortho Phosphate, Polyvinyl Alcohol, Hydrochloric Acid, Sodium Hydroxide, Water for injection

6.2 Incompatiblities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30^0C in a dry place. Protect from light. Do not freeze.

6.5 Nature and contents of container <and special equipment for use, administration or implantation

5 mL solution filled in 5 mL labelled LDPE Bottle and packed in a carton with pack insert.

6.6 Special precautions for disposal <and other handling>

No special requirement

7. APPLICANT/MANUFACTURER

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DRUG PRODUCT MANUFACTURER

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